

## REMARKS

### Introductory Comments

Reconsideration of the above-identified application in view of the above amendments and foregoing arguments is respectfully requested.

Claims 59, 61, 72-81 and 84 are pending and under consideration. Claims 57, 58, 60, 62, 76, 82 and 83 have been canceled in this amendment. Claims 59, 72, 77, 80-81 and 84 have been amended as explained below. No new matter has been added as a result of these amendments.

### Specification Amendment

The Examiner states that in Applicants' previous amendment to page 1 of the specification, the priority application 07/642,734 was incorrectly typed as "08,642,734". This typographical error has been corrected in this amendment. Applicants thank the Examiner for pointing out this error.

### Claim Objections

Claims 62 and 84 are objected for informalities.

Specifically, the Examiner states that claim 62 recites "dehydrataseand" which is a typographical error. The Examiner further suggests that a comma be inserted. Applicants have canceled claim 62 and the objection to this claim is now moot.

The Examiner states that "its" should be changed to "a" in clause (4) of claim 84. Applicants have amended claim 84 as suggested by the Examiner. Applicants thank the Examiner for his suggestion.

Claims 57, 58 and 73 are also objected to for the following reasons.

The Examiner states that these claims contain improper Markush groups because the compounds listed do not share a common utility or a substantial

structure that is essential to that utility. Applicants respectfully traverse this objection.

Applicants assert that the compounds listed in claim 58, which depends on claim 57, all share the common utility of having a polyketide synthase enzymatic activity and all share a structure of a polyketide synthase enzyme. Thus, claim 58 recites "wherein said polyketide synthase enzymatic activity is selected from the group consisting of...". Also, Applicants would like to direct the Examiner to page 19, where it states "Whether the genetic manipulations are performed in intraspecies or interspecies, three types of alterations to a PKS sequence may be carried out: (i) those which affect a module but do not cause arrest of chain growth ( $\beta$ -ketoreductase, dehydratase or enoylreductase) (Type I alterations); .... and (iii) those which affect an entire module (Type III alterations). In one embodiment, Type I alterations are produced by inactivation of domains that specify functional groups and/or degree of oxidation found at specific ring positions in the native polyketide. Such domains typically include  $\beta$ -ketoreductases, dehydratases and enoylreductases. For example, an allele corresponding to  $\beta$ -ketoreductase of module 5 may be mutated by deleting a substantial portion of the DNA encoding the  $\beta$ -ketoreductase (thereby producing an inactive domain) and used to replace the wild-type allele in the native strain. Such transfer results in the production of the novel polyketide 5-oxo-5, 6-dideoxy-3- $\infty$ -mycarosyl erythronolide B.". Therefore, the proteins listed have common domain structures as well as common enzymatic functions such as type I-III alterations.

The Examiner also states that claim 73 relates to genera sharing no substantial structure feature in their chromosomes. Applicants respectfully traverse this objection. Claim 73 now depends from claim 84 which requires a DNA sequence producing a polyketide, among other structural and functional characteristics as recited in claim 84. Applicants therefore submit that the claimed genus in the Markush group is proper.

In an effort to expedite prosecution of the instant application, claims 57 and 58 have been canceled as explained below. Applicants reserve the right to

prosecute the subject matter of these claims in one or more continuing applications.

For these reasons, Applicants respectfully request withdrawal of the objections of claims 62, 57, 58, 73 and 84.

#### Specification Objection

The specification was objected to as failing to provide proper antecedent basis for the claimed subject matter. Specifically, the Examiner states that the fourth, fifth and sixth compounds recited in claim 80 are not disclosed in the specification.

Applicants have amended claim 80 by deleting these compounds. Therefore, the objection is now moot. Applicants reserve the right to prosecute the subject matter of these claims in one or more continuing applications.

#### Election/Restriction

The Examiner imposes a restriction on the claims. Specifically, the Examiner states that claim 57, 58, 80, 82 and 83 specifically exceed the subject matters telephonically elected by Applicants on August 30, 2002. Claims 72-79 and 81 depend from claim 57 and therefore are also considered as exceeding the subject matter of Groups I and II which were elected (subject matter which the Examiner suggested for clauses 3(i) and 3(ii) in claim 84).

The Examiner states that Applicants are required to conform claim 57 to positively recite the elected alterations of polyketide synthase  $\beta$ -carbonyl processing functions – the inactivation or addition of  $\beta$ -ketoreductase, enoyltransferase, and dehydratase domains by altering a native polyketide synthase-encoding DNA sequence. The Examiner also requires Applicants to delete from claim 58, the non-elected “enzymatic activities” of “acyl carrier protein,  $\beta$ -ketoacyl ACP synthase and acyltransferase”, as well as to delete from claim 80, the compound 7-oxyerythromycin A and the six compounds at lines 4-6 of claim 80 which are not disclosed to result from a method of directing the biosynthesis of a polyketide analog by requiring addition or inactivation of any or

all of the inactivation or addition of  $\beta$ -ketoreductase, enoyltransferase, and dehydratase domains by altering a native polyketide synthase-encoding DNA sequence.

Finally, the Examiner states that because the activity of any acyltransferase domain is not involved in polyketide synthase  $\beta$ -carbonyl processing functions, Applicants are required to cancel claims 82 and 83 which describe polyketide analogs that the specification discloses to be prepared by one or more of DNA sequences encoding acyltransferase domains to genes encoding polyketide synthases.

In a prior communication, the Examiner placed a combination-subcombination restriction on the claims. Applicants therefore traversed the restriction and now maintain the traversal. Applicants respectfully submit that the Examiner effectively restricted the broad claims from the narrow claims without providing the proper reasons.

However, in an effort to expedite prosecution of the instant application, Applicants have canceled claims 57, 58, 82 and 83, and amended claim 80 in the manner suggested by the Examiner. As pointed out above, Applicants traverse the restriction imposed by the Examiner and their arguments are incorporated herein. Thus, Applicants reserve the right to prosecute the subject matter of these claims in one or more continuing applications, which have been deleted based on the restriction requirement instead of substantive issues.

Therefore, the restriction requirement is now moot.

#### Double Patenting Rejection

Claims 57-62, 72-75, 77-81 and 84 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 5,824,513.

Applicants enclose herewith a terminal disclaimer in order to obviate the double patenting rejection. Accordingly, Applicants respectfully request withdrawal of the double patenting rejection.

Rejection of Claims 57-62, 76-78 and 82-84 Under 35 U.S.C. § 112,

First Paragraph

Claims 57-62, 76-78 and 82-84 are rejected under 35 U.S.C. § 112, second paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection.

Specifically, the Examiner states that claim 57 describes methods for genetic manipulation of generic “polyketide biosynthetic gene-containing DNA sequences” from any and all polyketide-producing microorganism and claim 84 similarly describes methods of genetic manipulation of generic “DNA sequences... encoding polyketide synthase polypeptides” from any and all polyketide-producing microorganisms. However, the Examiner alleges that the specification only disclose manipulation of *Saccharopolyspora* species, *Streptomyces* species (page 43), *Micromonospora* species and *Nocardia* species, but not all microorganisms.

The Examiner also states that while the specification provides support for *Saccharopolyspora erythraea*, it does not provide support for *Saccharopolyspora hydroscopicus* of claim 76. Claim 76 has been canceled.

In the priority document, U.S. Patent Number 5,824,513, at column 3, lines 30-44, the term “polyketide-producing microorganism” is clearly defined to include any strains of *Micromonospora*, *Sacharapolyspora*, *Streptomyces*, *Actinomadura*, *Dactylosporangium* and *Nocardia* that produce polyether type of polyketides. This is also disclosed on pages 3, 4 and 10 of the instant application. Applicants submit that one of ordinary skill in the art would be able to determine which microorganisms fall into these categories by Applicants' teachings. Applicants further submit that it is not practical to provide detailed examples of every possible microorganism for the invention. Applicants further submit that claim 84, the only independent claim in the instant application, is drawn to a method for directing the biosynthesis of a specific polyketide analog.

The claim requires specific steps such as altering the DNA sequence encoding the polyketide synthase polypeptide by either or both of the step (i) disrupting the DNA sequence and (ii) inserting within the DNA sequence. The claim also requires the transforming step (4) of a polyketide-producing microorganism. This claim was suggested by the Examiner and Applicants have conformed to all of the requirements set forth by the Examiner. Thus, Applicants submit that through their novel and nonobvious steps of altering the DNA sequence encoding the polyketide synthase polypeptide, claim 84 pertains to only those microorganisms that can be altered through those steps and one of ordinary skill in the art would be able to recognize which microorganisms the method pertains to based on the level of knowledge necessary for a skilled artisan in microbiology. Therefore, Applicants respectfully submit that the claims are not unduly broad and appreciate any suggestion the Examiner may have that will not unduly limit the claims.

With respect to claim 80, the Examiner states that the specification and the priority documents do not disclose the fourth, fifth and sixth compounds. With respect to claims 82 and 83, the Examiner reiterates his position as stated above that there is no disclosure or suggestion of rapamycin analogs affecting  $\beta$ -carbonyl processing. Applicants have deleted the fourth, fifth and sixth compounds from claim 80 and canceled claims 82 and 83 as stated above. The rejection of these claims is now moot.

The Examiner also discussed the *Wands* factors by stating that:

- a) the specification lacks adequate, specific, guidance for specific genetic manipulation to alter the amino acid sequences of discontinuous polypeptides accepting any conceivable starter or extender units wherein one or more modules might be altered to direct the biosynthesis of any specific polyketide analog other than an erythromycin analog,
- b) the specification lacks working examples wherein genes encoding integral, or discontinuous, polyketide synthase polypeptides beyond an

erythromycin PKS are altered to the extent recited in the claims to produce a specific polyketide analog,

- c) in view of the prior art publications of record herein, the state of the art and the level of skill in the art do not support such alteration, and
- d) unpredictability exists in the art where no members of other classes of PKS polypeptides have been altered to direct the biosynthesis of specific analogs of polyketides other than erythromycin.

Applicants respectfully traverse the rejection based on these arguments. In *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), the Court of Appeals for the Federal Circuit discussed the issue of undue experimentation. The Court states that in order for the specification to be enabling, it must teach those skilled in the art how to make and use the full scope of the invention without undue experimentation. However, the Court also states that there can be some experimentation required and the specification is still enabling. *Id.* The Court provides the following factors only in determining whether a specification is enabling in unclear cases: 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the predictability or unpredictability of the art, and 7) the breadth of the claims. *Id.*

With respect to the first factor, Applicants submit that the quantity of experimentation is not necessarily high for the claimed invention. Steps (i) and (ii) of claim 84 require disrupting the DNA sequence encoding the polyketide synthase in one or more regions encoding a domain providing a  $\beta$ -carbonyl processing enzymatic activity selected from the group consisting of  $\beta$ -ketoreductase, dehydratase, and enoylreductase, the disruption resulting in inactivation of said enzymatic activity in polyketide biosynthesis, or inserting within the DNA sequence encoding the polyketide synthase one or more DNA sequences encoding a domain providing  $\beta$ -carbonyl processing enzymatic activity selected from the group consisting of a  $\beta$ -ketoreductase, dehydratase, and enoylreductase, the insertion resulting in the addition of said enzymatic

activity in polyketide biosynthesis. Although one of ordinary skill in the art would not be able to recognize the benefits of the invention as a whole unless disclosed by Applicants, one of ordinary skill in the art would know what is a DNA sequence that encodes a polyketide synthase which encodes a  $\beta$ -carbonyl processing enzymatic activity selected from the group consisting of  $\beta$ -ketoreductase, dehydratase, and enoylreductase, the disruption resulting in inactivation of said enzymatic activity in polyketide biosynthesis, how to disrupt this DNA sequence, and the results from such. One of ordinary skill in the art would likewise recognize and appreciate step (ii) in a similar manner.

With respect to the second factor, the amount of direction or guidance provided by Applicants is not necessarily high and the amount of direction or guidance from the specification is adequate. Applicants provide working examples of the invention such as those for the erythromycin analogs. Applicants submit that one of skilled in the art would appreciate the direction and guidance with respect to these analogs as provided by Applicants and apply them to other analogs having similar structural and functional characteristics.

With respect to the third factor, there is a presence of working examples provided in the specification instead of an absence of working examples. As noted above, Applicants provide a number of working examples for the erythromycin analogs.

With respect to the fourth factor, the nature of the invention is not complex and not considered a new or emerging technology. The *M.P.E.P.* § 2164.03 states that the level of knowledge in an art indicates the level of predictability. In *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362 (Fed. Cir. 1999), the Court of Appeals for the Federal Circuit states that consideration of an invention in a new technology impacts on how the *Wands* factors are evaluated. The Court also states that the unpredictable arts include areas of technology and research that require further development and understanding. *Id.* at 1372. Applicants submit that although other areas of biotechnology are new and unpredictable, the specific area of technology which Applicants invention pertains is not complex such that undue experimentation is likely required to carry out Applicants'



invention. Although the application of the claimed steps are novel and non-obvious as a whole, the individual steps such as gene disruption, DNA insertion, and inactivation or activation of enzymatic activities in a polyketide synthesis via specific enzymes are recognizable and understood by one of ordinary skill in the art.

With respect to the fifth factor, the state of the prior art is mature as discussed above under factor four. The result is that with the amount of information provided in the specification, one of ordinary skill in the art would be able to make and/or use the invention.

With respect to the sixth factor, there is predictability in disrupting or inserting DNA sequences in specific regions of a specified gene to a certain degree although Applicants' invention is novel and non-obvious. As noted above, Applicants have provided direction and guidance as to which genes are involved, which enzymes are involved and which enzymatic activities are involved in the claimed steps. Although no method have been performed using all of the steps as claimed, there is no reason for one of ordinary skill in the art to question the method as disclosed in the instant specification. Applicants submit that the many working examples provided in the specification provide detailed information such that the amount of unpredictability is acceptable.

Finally, the breadth of the claims are not overly broad. As noted above, Applicants have amended the claims to provide detailed steps as suggested by the Examiner in the previous Office Action.

For these reasons, Applicants respectfully request withdrawal of the rejection of claims 57-62, 76-78 and 82-84 under 35 U.S.C. § 112, second paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Rejection of Claims 57-62 and 72-84 Under 35 U.S.C. § 112,

Second Paragraph

Claims 57-62 and 72-84 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner points out a number of problems with the claim language of claim 57. Applicants have canceled claim 57 such that the rejection of this claim and its dependent claims for the indefiniteness of claim 57 is now moot.

Applicants would like to point out to the Examiner that as claim 57 has been deleted, the dependent claims have been amended to depend from claim 84, the only independent claim remaining, accordingly.

For these reasons, Applicants respectfully request withdrawal of the rejection of claims 57-62 and 72-84 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants would like to thank the Examiner for his thorough examination of the instant application. Applicants would appreciate any suggestions the Examiner may have such that the prosecution of the instant application is expedited.

## CONCLUSION

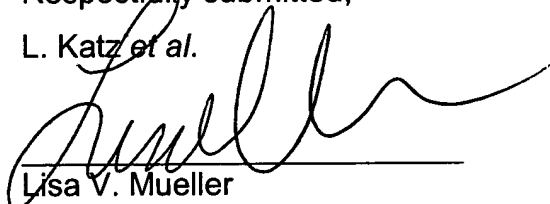
Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Section 112. Accordingly, a Notice of Allowance is believed to be in order and is respectfully requested.

Should the Examiner have any questions concerning the above, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account no. 23-0785.

Respectfully submitted,

L. Katz et al.

A handwritten signature in black ink, appearing to read 'Lisa V. Mueller', is written over a horizontal line.

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